

CONTINUING MEDICAL EDUCATION

# The Pathophysiology, Diagnosis, and Treatment of Constipation

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## SUMMARY

**Background:** Constipation is a common condition about which there are many widespread notions that have no basis in fact. The purpose of this article is to summarize current scientific knowledge on the subject.

**Methods:** Selective review of the literature.

**Results:** Diagnostic evaluation usually fails to reveal the cause of constipation. It is due to medications in some patients, while endocrine disorders are the cause in only a small minority. Abnormal defecation may be due to dysfunction of the pelvic floor. Most patients complain of abdominal fullness and of needing to strain to pass stool; low stool frequency is a rare symptom. The symptoms alone determine the indication for treatment. Constipation usually poses no threat to health. Some patients are helped by a diet rich in fiber, others by laxatives. A number of laxatives with different modes of action are available; all are safe and generally well tolerated. In some patients, dysfunctional defecation may be an indication for proctological surgery.

**Conclusions:** The Rome criteria are useful for establishing a specific diagnosis of constipation. Most patients can be helped with laxatives and patient education.

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**Key words:** constipation, defecation, laxatives, dietary fiber

**C**hronic constipation goes under a number of alternative designations, including "irregularity," "costiveness," "sluggishness of the bowels," and "intestinal hypomotility." The treatment of constipation with bowel movement–inducing procedures and medications has a long history. Many unproven notions, some of them demonstrably false, are in circulation even today regarding the causes and treatment of constipation. When polled, 10% to 20% of persons in the general population state that they suffer from constipation (1).

The learning objectives of this article for the reader are the following:

- knowing the symptoms to which the term "constipation" refers, and understanding their causes;
- knowing which diagnostic studies are indicated (and which are superfluous);
- being able to identify incorrect notions about the significance of constipation and about its treatment;
- being able to advise sufferers about the significance and treatment of constipation.

This review article is based on a search of the PubMed database for articles containing the key word "constipation."

## Definition

The term "constipation" refers to a constellation of symptoms. Only one-quarter of all patients who consider themselves constipated state that they have fewer than three bowel movements per week (2). Some patients are worried that their stool frequency is too low because they fear self-poisoning in consequence of the long time that the stool remains in the body; this fear has no basis in fact (3). For most patients, the chief complaint is either a feeling of fullness and/or the need to strain in order to have a bowel movement.

The "Rome criteria" are a useful set of diagnostic criteria for constipation that highlight the chronicity of the

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## Definition

The term "constipation" refers to a constellation of symptoms.

## BOX 1

### The diagnosis of constipation according to the current version of the "Rome criteria"

At least two of the following symptoms are required to have been present for at least three of the past six months (2):

- Straining at stool at least 25% of the time
- Hard stools at least 25% of the time
- A feeling of incomplete evacuation at least 25% of the time\*<sup>1</sup>
- A feeling of anal blockage at least 25% of the time\*<sup>1</sup>
- Manual maneuvers for rectal emptying at least 25% of the time\*<sup>1</sup>
- Two stools or less per week

\*<sup>1</sup> These symptoms indicate an impairment of defecation

TABLE 1

### Medications that commonly cause constipation, and the appropriate therapeutic management

Constipating medication	Therapeutic management* <sup>1</sup>
Antihypertensive agents (calcium antagonists, clonidine)	Changing the active substance (e.g., ACE inhibitors, beta-blockers)
Tricyclic antidepressants	SSRI (selective serotonin reuptake inhibitors)
Iron preparations	IM or IV administration, or laxatives
Antiepileptic drugs	Laxatives
Opiates	A combination of oxycodone with naloxone, or methylnaltrexone,* <sup>2</sup> or laxatives
Antiparkinsonian agents (Anticholinergic or dopaminergic)	Laxatives

\*<sup>1</sup> A change of preparation is useful for some medications, while for others only the additional administration of a laxative will give benefit. Of course, one should first try to discontinue the offending medication or lower the dose;

\*<sup>2</sup> These are the only measures that have been shown to be effective in randomized, controlled studies (6, 7)

## BOX 2

### The pathophysiological components of chronic constipation

- Abnormal intrinsic motility
- Lack of luminal factors (stretching, chemical and tactile stimuli)
- Medications (see Table 1)
- Hormones (very rarely, e.g., in pheochromocytoma)
- Lack of extrinsic innervation (in paraplegia)
- Impaired defecation

disorder and the importance of symptoms other than infrequency of bowel movements. They serve the purpose of cutting back on unnecessary ancillary diagnostic testing (Box 1). They are also intended to enable more uniform reporting of therapeutic trials (2).

### Pathogenesis

A variety of pathogenetic mechanisms can cause constipation (Box 2). The distinction between organic and functional types of chronic constipation has no practical relevance in the treatment of patients.

### General lifestyle and nutrition

In a normal, non-constipated individual, physical activity can serve as a stimulus to bowel emptying. Ambulatory patients suffering from constipation are, however, no less physically active than healthy persons (3). Thus, telling a constipated patient to exercise more is illogical. Neither are such recommendations founded in any demonstration of efficacy.

Although it is true that a diet including little dietary fiber is associated with low stool volume in healthy persons, dietary analysis does not reveal any difference in the amount of dietary fiber consumed by constipated and non-constipated persons (3). Bacterially non-degradable dietary fiber, such as wheat bran, has been found in meta-analyses to improve transit time and stool weight, yet constipated persons have, on the average, low stool weight and prolonged transit times regardless of whether their diet contains a large amount of fiber (4).

### Prolonged colonic transit time

Some constipated persons can be shown to have a prolonged colonic transit time that cannot be normalized even by the consumption of large amounts of dietary fiber. This is true of about half of all patients (5) in specialized centers, but presumably fewer in general practice.

In occasional cases, constipation is due to an underlying endocrine or, more commonly, neurological disease; in other cases, it is an undesired effect of medication (Table 1). Opiate-induced constipation, in particular, should be treated as soon as it arises (6). In most cases, however, the cause remains unclear. The importance of hormonal causes is generally overestimated (except during pregnancy). About half of all premenopausal women report having less frequent bowel movements in the second half of their cycles, but the objectively measurable transit delay is only slight (3). Parkinson's disease and paraplegia are the main neurological causes.

### Symptoms

Low stool frequency is only one of the symptoms of constipation. There is no minimum stool frequency required for good health.

### Possible causes of secondary constipation

Secondary forms of constipation are often due to neurological causes and only rarely due to endocrine causes.

TABLE 2

**The most important laxatives and their main advantages and disadvantages**

Class* <sup>1</sup>	Example (Dose)	Mechanism of action	Disadvantages
Salts (saline laxatives)	<ul style="list-style-type: none"> <li>Glauber's salt, Epsom salt (10 g)</li> <li>Carlsbad salt, MgOH (5 g)</li> </ul>	<ul style="list-style-type: none"> <li>Osmotic water binding</li> </ul>	Electrolyte disturbance, possible abdominal discomfort, bad taste, continued use?
Soluble macromolecules	<ul style="list-style-type: none"> <li>Macrogol (10–20 g)</li> </ul>	<ul style="list-style-type: none"> <li>Osmotic water binding</li> </ul>	Possible bad taste, mainly when used over the long term and when salt-containing preparations are used
Sugars	<ul style="list-style-type: none"> <li>Lactulose, sorbite (10–30 g)</li> </ul>	<ul style="list-style-type: none"> <li>Osmotic water binding, bacterial mass</li> </ul>	Not very effective against severe constipation; increased formation of abdominal gas
"Stimulants"	<ul style="list-style-type: none"> <li>Bisacodyl, picosulfate (5–10 mg)</li> <li>Senna (10–20 mg)</li> </ul>	<ul style="list-style-type: none"> <li>Prokinetic and antiabsorptive/secretagogic properties</li> <li>Anthraquinones and picosulfate are bacterially activated in the colon</li> </ul>	Possible abdominal discomfort; sometimes, habituation

\*<sup>1</sup> Members of each class of laxative have been found effective in randomized, controlled trials

## Impairment of defecation

Unlike mechanical obstruction of the intestinal lumen by neoplasms (for example), changes in the shape of the anorectum and pelvic floor and abnormalities of sphincter function can lead to a functional obstruction of the defecation pathway, and thus to constipation (8). Such changes can only be detected with functional diagnostic testing, e.g., by functional proctological examination and defecography, rather than with traditional morphological techniques such as colonoscopy and positive-contrast colonic enema.

Some patients involuntarily contract the external anal sphincter while straining at stool and thereby block the defecation pathway (dyssynergy of the pelvic floor; anismus; so-called "outlet obstruction"). This is a case of faulty use of a muscle that is, in and of itself, normal. It is still unclear when or how this problem arises. Paradoxical contraction of the external sphincter can be demonstrated by a number of methods, including manometry, electromyography (EMG), and defecography, but any "pathological" finding of this type may be an artifact, because the patient is not as relaxed in the laboratory setting as he or she would be at home.

If the rectum is not held adequately in place while the patient strains at stool, invagination of the rectum can result (internal rectal prolapse). The invaginated segment of the bowel may then simulate a full rectum, so

that the patient feels the need to defecate (feeling of incomplete emptying) and strains further. Mechanical damage of the invaginated bowel wall is thought to be the cause of solitary rectal ulcers.

With larger rectoceles, and in cases of abnormal lowering of the pelvic floor, the pressure of straining serves only to expand the rectocele or push the pelvic floor further downward, rather than being employed, as it is normally, to widen the anal canal and expel the stool. These two pathological conditions are caused by trauma during childbirth and by chronic straining.

## Diagnostic evaluation

It is important that the patient's history should be taken actively, because patients often do not report certain symptoms spontaneously (Box 2). Apart from history-taking, diagnostic testing can be kept to a bare minimum for the vast majority of patients. A digital rectal examination is part of the basic physical work-up, particularly when the symptoms point to a possible functional disturbance of the rectum (Box 2). Colonoscopy is indicated only if an organic disease of the colon is suspected, or if it is due to be performed anyway for carcinoma screening. It is not an essential element of the diagnostic evaluation of chronic constipation. Laboratory studies, too, are superfluous in most cases.

## Impaired defecation

Possible impairment of defecation should be sought by specific questioning of the patient and directed physical examination.

## Causes of impaired defecation

Impaired defecation may be due to dysfunction of the anal sphincter or a pathological change in the architecture of the pelvic floor.

The next step is high-dose trial therapy with bacterially non-degradable dietary fiber, for a period of about two weeks. The most suitable substances for this purpose are wheat bran and psyllium preparations. Bran is less expensive, but also less well tolerated (9). If a trial of non-degradable fiber results in adequate improvement of the symptoms, then no further diagnostic assessment is needed (5). Measurement of the transit time mainly serves to objectify the patient's symptoms, as subjective reports of low stool frequency are often not very accurate. If the transit time is normal, for example, then this will effectively disprove a patient's claim of having had "practically no bowel movements at all for a week."

Suspected impairment of defecation is best evaluated by defecography. In this testing technique, a viscous barium suspension is instilled into the rectum, and rectal emptying is documented with lateral pelvic fluoroscopy while the patient defecates into a radiolucent plastic commode (10). This test involves a certain amount of exposure to radiation that must be borne in mind, particularly when the patient is a woman of child-bearing age.

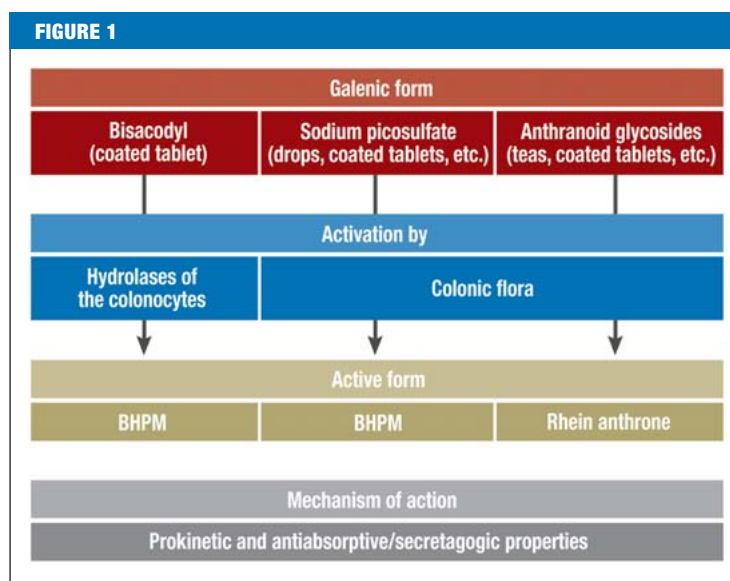
## Treatment

Chronic constipation is generally harmless, but it often impairs the patient's quality of life (11). Diagnostic evaluation and treatment are needed only when the patient's subjective degree of suffering calls for it.

### Basic treatment

Patient education is important. The physician should explain to the patient that there is no minimum required frequency of bowel movements, and that rarity of bowel movements is not known to be associated with any health problems (there is no such thing as "autointoxication" or self-poisoning with unpassed stool) (3). If trial therapy with dietary fiber is successful and well tolerated, it is reasonable to recommend a high-fiber diet with whole wheat products. Fruit and vegetables are relatively ineffective, because most of the dietary fiber they contain is degraded by bacteria (12).

A number of proposed treatments for chronic constipation continue to be uncritically recommended, in textbooks as well, even though they have not been shown to be effective or have actually been shown to be ineffective. While plausible physiological mechanisms can be adduced for some of these recommendations (eat breakfast to induce colonic motility, then allow sufficient time for a visit to the toilet), others lack even this degree of plausibility (drink more than "normal" persons, e.g.,



The pharmacology of stimulating laxatives. BHPM; bis-(p-hydroxyphenyl)-pyridyl-2-methane

more than 1.5 liters per day; engage in vigorous exercise) (3). It is likewise incorrect to imagine that bran and other high-fiber foods need to be taken with additional liquid (3).

## Laxatives

It is not known how many patients can be adequately treated with the measures discussed above. Undoubtedly, some patients do need pharmacotherapy; many obtain laxative medications themselves without a prescription. Once basic therapy has been tried and found to be unsuccessful, there is no medical objection to the long-term use of laxatives. The "laxative colon" that was observed in an earlier era was probably due to the neurotoxic substance podophylline (13). An overview of the laxatives in use today is provided in *Table 2*.

### Water-binding laxatives

Some osmotic salts, such as Carlsbad salt, are found in natural sources and have been used to treat constipation for many years. They have hardly been studied systematically but are probably safe, except in the presence of chronic renal failure or congestive heart failure (14). If they are used over the long term, their bad taste may be a problem.

In recent years, polyethylene glycol (molecular weight 3350–4000, macrogol), which has long been

## Psyllium

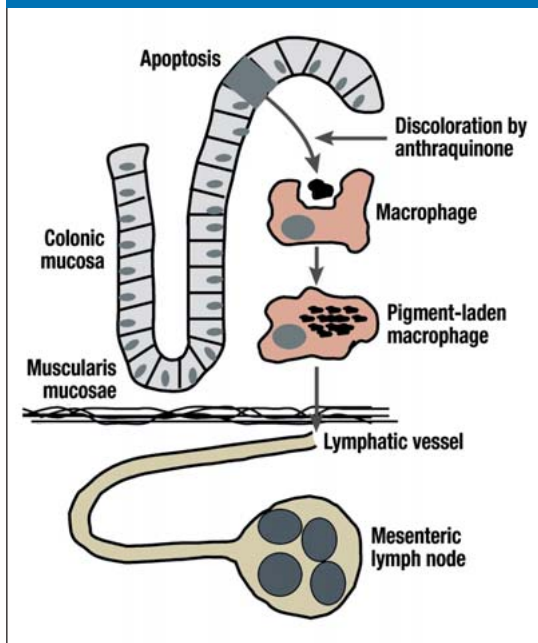
High-dose trial therapy with bacterially non-degradable dietary fiber can be carried out, for example, with psyllium preparations.

## Unsupported hypotheses

A number of proposed treatments for chronic constipation continue to be uncritically recommended, in textbooks as well, even though they have not been shown to be effective or have actually been shown to be ineffective.

Melanosis coli: epithelial cells migrating toward the submucosa in the process of apoptosis obtain a black color from anthraquinone and are then phagocytosed. The macrophages take on the black pigment and then migrate away by way of the lymphatic vessels.

FIGURE 2



used to cleanse the bowel in preparation for diagnostic and therapeutic procedures, has been found to be effective for the long-term treatment of constipation (15). Macrogol should be taken daily. Its onset of action is relatively slow, and tolerance does not appear to develop. The electrolytes found in many preparations are not an advantage.

The sugar alcohol sorbitol and the disaccharide lactulose are also often used to treat constipation. They produce a considerable degree of bloating, however, and are not very effective if the colonic transit time is prolonged (15, 16).

#### Stimulating laxatives

The generic term "stimulating laxatives" includes the anthraquinones as well as the diphenylmethanes bisacodyl and sodium picosulfate. These agents have a dual mechanism of action. They inhibit fluid resorption from the small and large intestines and induce fluid secretion in dose-dependent fashion; they also have a marked prokinetic effect. The latter may cause cramp-like abdominal pain. These medications take effect 6 to 12 hours after they are consumed, causing one to three bowel movements (17). Stimulating laxatives (bisacodyl, picosulfate, anthraquinones) need not be taken daily, and one or two

doses per week may suffice. Chronic overdosing can be expected to produce side effects, but administration in the recommended dose will not cause any untoward effects. In particular, proper dosing does not cause hypokalemia, even though this concern is often voiced. Some patients say that they develop tolerance to these preparations and therefore switch to a different one every so often, but this matter has not been systematically studied. A Swedish study involving a retrospective questionnaire revealed that about half of all patients moderately increased the dose of picosulfate over years of use, but they did not take more than the maximum recommended dose. Some patients, however, were actually able to lower the dose (18).

Anthraquinones are naturally present in the form of glycosides. These compounds cannot be resorbed from the small intestine and thus have no effect on it. The pharmacologically active rhein anthrones arise only in the colon as the result of bacterial degradation of the drug (Figure 1). A number of different anthraquinone preparations are now commercially available; the pure sennosides have been the most thoroughly studied (16). The "purely natural" origin of these substances is often stressed in advertisements but confers no known advantages or disadvantages. No association between the use of anthraquinones and colon carcinoma was found in any of the epidemiological studies that have addressed this question (19). Nor is there any danger of damage to the autonomic nervous system. The brown discoloration of the colonic mucosa that is seen after anthraquinone use (melanosis coli) is of no functional significance (3). Epithelial cells migrating toward the submucosa in the process of apoptosis obtain a black color from anthraquinone and are then phagocytosed; the macrophages take on the black pigment, then migrate away by way of the lymphatic vessels, so that melanosis resolves some time after anthraquinone use is discontinued (Figure 2).

The synthetic laxative bisacodyl is converted into the active substance BHPM (bis-[p-hydroxyphenyl]-pyridyl-2-methane) by hydrolases of the colonic mucosa. Because an effect on the small intestine is not wanted, this medication is given only in tablet form, and not in liquid form. An elegant alternative is to administer the sulfate ester of bisacodyl, i.e., sodium picosulfate (17). This substance is enzymatically activated by hydrolases only after it is degraded by bacteria in the colon. It can thus be given in drop form and can be more finely dosed.

Rectal varieties of constipation can be treated with bisacodyl and, for example, glycerine in suppository

#### Melanosis coli

Brown discoloration of the colonic mucosa after the ingestion of anthraquinones (melanosis coli) is of no functional importance.

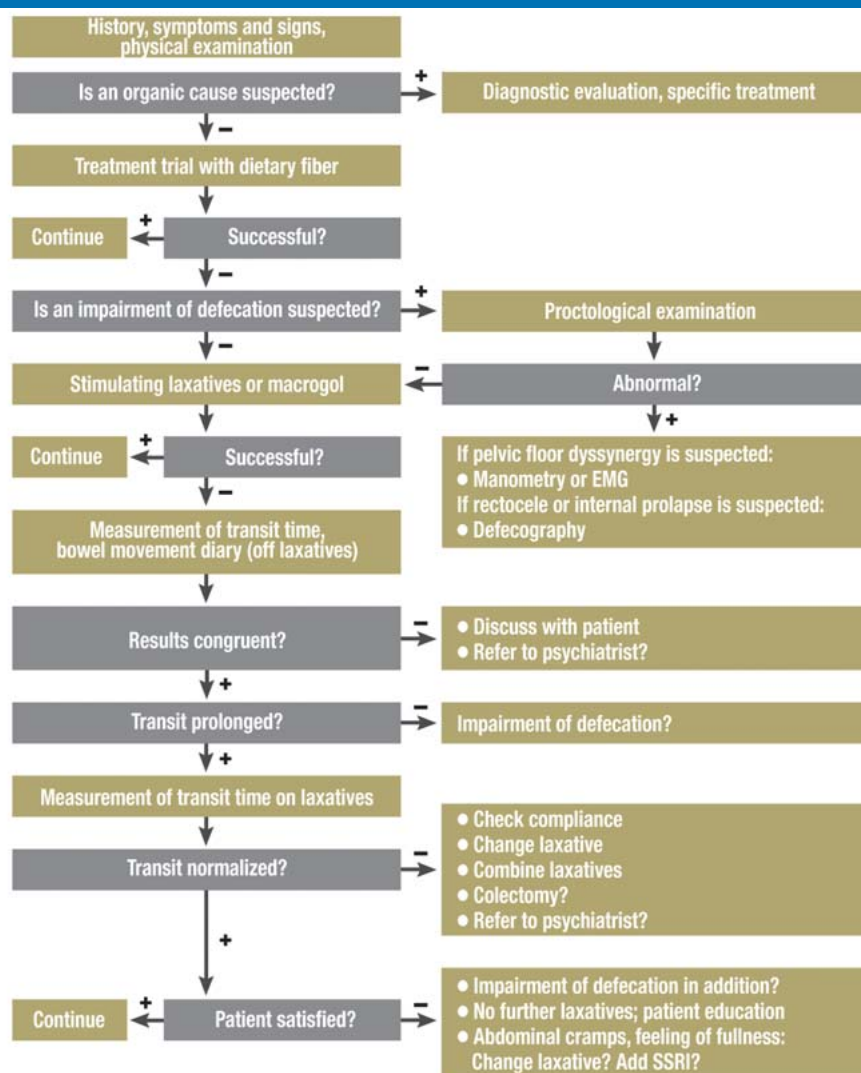
#### Prokinetic agents

A direct prokinetic effect on the colon has been demonstrated for:

- senna preparations
- bisacodyl
- pruclopride, tegaserod, and cisapride



**FIGURE 3**



Recommended diagnostic and therapeutic algorithm for constipation

form. The patient's preference is determinative, however, not just regarding the mode of administration, but also regarding the substance used. When the problem is an impairment of defecation that has been unambiguously demonstrated by defecography, a proctological surgical intervention can be considered. Colectomy can be considered in rare cases of slow colonic transit that does not respond to treatment with laxatives.

#### Prokinetic agents

Because chronic constipation is usually a hypomotile disorder, it would seem logical to attempt to treat it with purely prokinetic agents. In accordance with our current state of knowledge, the main purely prokinetic agents coming into consideration are 5-HT<sub>4</sub> agonists. In this class of medications, cisapride, prucalopride, and tegaserod have been well studied in randomized, controlled trials and have been found to be moderately

#### Effectiveness

At present, the stimulating laxatives and macrogol have the best ratio of beneficial effects to side effects.

#### Successful treatment

Most patients can be treated satisfactorily with dietary fiber and/or laxatives.

effective against chronic constipation (20). Cisapride and tegaserod have, however, been taken off the market in the meantime because of safety concerns. It is possible that prucalopride will be approved within the coming year.

### Disimpaction

Fecal impaction (coprostasis) deserves special mention because it is a common problem, especially among elderly inhabitants of nursing homes. Particularly in immobile patients, large quantities of stool may clump together in solid masses (coproliths) in the lower colon. Stretching of the rectum causes relaxation of the internal anal sphincter, and fluid stool flows out past the solid fecal bolus. The problem often goes unrecognized or misdiagnosed for a long time, even though digital rectal examination immediately reveals the diagnosis. The "traditional" treatment is by manual disimpaction, for which intravenous sedation of the patient is often required. The oral administration of macrogol (ca. 100 g in 1 liter of fluid per day) can also alleviate the problem in two to three days. It is important to prevent recurrent coprostasis thereafter by regular treatment of the underlying chronic constipation with suitable laxatives. Bran is not appropriate for this purpose.

### New developments

Lubiprostone stimulates intestinal chloride secretion and has been shown effective against chronic constipation in randomized, controlled studies (21), but it has not yet been approved for use in Europe. Linaclotide, a guanylate cyclase C agonist that stimulates intestinal secretion and transit (22), also still awaits approval.

### Psychophysiological techniques

Pelvic floor dyssynergy was improved with the aid of biofeedback training in about half of all patients studied in randomized, controlled trials (23). The effectiveness of this method in non-rectal constipation is difficult to assess, because only uncontrolled trials have been published (24). Biofeedback training is also highly labor-intensive. Women complaining of constipation show an elevated degree of psychological morbidity, with an abnormal perception of self and an increased prevalence of partnership problems (25). No systematic studies have yet been performed, however, regarding the possible effect of psychotherapy on constipation (although such studies have been done for irritable bowel syndrome).

### Overview

Constipation can be reliably diagnosed with the aid of the Rome criteria (*Figure 3*). Organic disease of the colon usually does not manifest itself as chronic constipation. Colonoscopy can, therefore, be dispensed with if there is no other reason to perform it. There is no reason whatever for multiple colonoscopies. The "general measures" that are often recommended are of dubious efficacy. Dietary fiber is worth trying, but it is not a magic bullet, and some patients cannot tolerate it. The available laxatives are effective and safe. The choice of laxative is based on the type of constipation that is present, as well as on the patient's individual tolerance profile and preferences. The stimulating laxatives and macrogol have the best ratio of beneficial effects to side effects. Purely prokinetic agents are not yet on the market. Even though—or precisely because—laxatives are available without a prescription, the physician has a very important role to play in advising the patient about the best ones to use and the proper doses to take them in.

#### Conflict of interest statement

The author has been, or is currently, a consultant for the following companies: Axcan Pharma, Boehringer Ingelheim, Menarini Pharmaceuticals, Movetis NV, Mundipharma GmbH, Pfizer Ltd., Procter & Gamble, Sucampo Pharma, and Zeria Pharma.

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The solutions to the following questions will be published in volume 31–32/2009. The CME unit "Differential Diagnosis of Food Intolerance" (issue 21/2009) can be accessed until 3 July 2009.

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### Question 1

**Which of the following pieces of information is most important for establishing the diagnosis of "chronic constipation"?**

- a) Measurement of the colonic transit time
- b) Measurement of the stool volume
- c) Stool coloration
- d) The patient's description of the symptoms and their duration
- e) Stool consistency

### Question 2

**Which of the following medications can promote constipation?**

- a) Opiates, corticosteroids, and calcium antagonists
- b) Opiates, calcium antagonists, and tricyclic antidepressants
- c) Calcium antagonists, proton-pump inhibitors, and antibiotics
- d) Proton-pump inhibitors, tricyclic antidepressants
- e) Opiates, beta-blockers, and antihistamines

### Question 3

**Which of the following is an indication for treating chronic constipation?**

- a) The danger of autointoxication from prolonged retention of stool in the colon
- b) The elevated risk of colon carcinoma in persons suffering from constipation
- c) The patient's subjective complaints
- d) The low frequency of bowel movements
- e) There is no valid indication for treating chronic constipation

### Question 4

**The dietary-fiber component of which of the following foods has a particularly marked influence on stool volume?**

- a) Apples
- b) Chocolate
- c) Whole-wheat products
- d) Fruit juices
- e) Whole milk

### Question 5

**Which of the following substances are considered "stimulating laxatives"?**

- a) Anthraquinones and macrogol (polyethylene glycol)
- b) Lactulose and Glauber's salt (decahydrated sodium sulfate)
- c) Epsom salt (heptahydrated magnesium sulfate), Glauber's salt, and bisacodyl
- d) Bisacodyl, picosulfate, and anthraquinones
- e) Macrogol and picosulfate

### Question 6

**Which of the following substances have been shown to have a direct prokinetic effect on the colon?**

- a) Senna preparations, bisacodyl, and prucalopride
- b) Lactulose, bisacodyl, and prucalopride
- c) Bisacodyl, wheat bran, and prucalopride
- d) Glauber's salt, senna preparations, and tegaserod
- e) Macrogol, lactulose, and Epsom salt

### Question 7

**What side effects can be expected from the use of anthraquinones, even when taken as recommended?**

- a) Hypokalemia
- b) Colon carcinoma
- c) Increased gas formation
- d) Diminished resorption of other glycosides, e.g., digitoxin
- e) Abdominal discomfort

### Question 8

**What is melanosis coli?**

- a) Irreversible discoloration of the colonic mucosa
- b) Epithelial damage due to anthraquinones
- c) A precancerous condition
- d) A regular sequela of the use of laxatives
- e) Discoloration of submucosal macrophages

### Question 9

**Which of the following laxatives has the named side effect even when taken in the correct dose?**

- a) Glauber's salt—hypokalemia
- b) Lactulose—increased gas formation
- c) Macrogol—abdominal cramps
- d) Bisacodyl—dependence
- e) Sennosides—colon carcinoma

### Question 10

**What is/are the usual cause(s) of large rectoceles and/or abnormal lowering of the pelvic floor?**

- a) Excessive consumption of laxatives in high doses
- b) Long-term, (almost) daily laxative consumption
- c) Trauma during childbirth and chronic straining at stool
- d) The consumption of constipating medications
- e) Crohn's disease and ulcerative colitis